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APPETITE-REGULATING HORMONES IN ENERGY COMPENSATION WITH EXERCISE

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APPETITE-REGULATING HORMONES IN ENERGY COMPENSATION WITH EXERCISE

THESIS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Nutrition and Food Systems in the College of Agriculture, Food and Environment at the University of Kentucky

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2020

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ABSTRACT OF THESIS

APPETITE-REGULATING HORMONES IN ENERGY COMPENSATION WITH EXERCISE

Background: The appetite-regulating hormones may influence compensatory increases in energy intake with exercise, although this causal relationship has been difficult to prove in a longitudinal trial.
Methods: 37 participants (29 female) aged 18 to 40 years performed aerobic exercise 6 days (6d), 2 days (2d), or 0 days per week for 12-weeks. Concentrations of ghrelin, leptin, glucagon-like peptide 1 (GLP-1), and insulin were assessed before (fasting, minute 0) and after a standardized meal at minute 15, 30, 45, 60, 90, 120, 150, and 180. Linear mixed-effects models were used to model the relationships between time point (12 weeks vs. baseline) and group over time (minutes 0 to 180) for each hormone. For 2d and 6d, the total area under the curve (AUC) for post-prandial hormone changes from pre-intervention to post was calculated and used to predict % body fat lost and energy compensation, defined as the difference between expected weight loss (based on exercise energy expenditure, ExEE) and changes in bodily energy stores. Energy compensation was expressed as % energy compensated (compensation index, CI).
Results: The 2d and 6d expended 1,490.7 ± 122.1 and 2,750.5 ± 145.1 kcal while exercising 188.8 ± 4.12 and 320.5 ± 3.7 min/week respectively (means ± SE, $P<0.01$). CI did not differ between 2d and 6d ($P=0.81$), averaging 52%. Only 6d lost significant body fat (-7.29% ± 2.13 vs -1.86% ± 4.12, $P=0.03$). For the mixed-effects model, ghrelin ($P=0.03$) and leptin ($P<0.01$) had significant group by time interactions, decreasing to a greater extent in 6d than 2d or control. Changes in AUC for ghrelin (delta-AUC) predicted the percentage of fat loss controlling for CI and ExEE while changes in AUC for leptin predicted CI controlling for ExEE and fat loss.
Conclusion: The 12-week changes in ghrelin and leptin are influenced by exercise frequency in overweight to obese adults. Greater decreases in ghrelin delta-AUC are an independent predictor of body fat loss attenuation, while greater leptin delta-AUC decreases are an independent predictor of CI. These findings represent a novel predictor of energy compensation and body fat loss with exercise.

KEYWORDS: Aerobic exercise, Weight loss, Energy compensation, Hunger hormones

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CHAPTER 1. Introduction

1.1 Background

Overweight (Body Mass Index [BMI] 25.0-29.9) and obesity (BMI ≥ 30.0) is a growing epidemic, with over 70% of the United States population classified as overweight or obese [1-4]. Obesity is a well-known risk factor in developing severe comorbidities such as heart disease, type 2 diabetes, fatty liver disease, and certain types of cancers, leading to early mortality [1, 2, 5]. The underlying cause of obesity is excessive weight gain through excessive energy intake and/or insufficient energy expenditure [5-7]. Energy intake has been observed to be influenced by physiological, genetic, environmental, and social factors. However, recent literature has demonstrated that physiological factors have the most significant impact [8, 9].

A commonly used obesity treatment strategy is exercise, increasing energy expenditure to favor a negative energy balance. However, exercise may also influence certain physiological factors, such as hormonal mediators of hunger, causing increases in energy intake; therefore, compensating for energy expended through exercise to resist desired weight loss.

1.2 Problem Statement

Many long-term and acute studies have investigated how different types of variables of an exercise program affect the concentrations of the appetite-regulating hormones and energy intake; however, the amount of research investigating the long-term consequence of these hormonal alterations is little to none [10-17]. Therefore, investigating the effect of exercise frequency on appetite-regulating hormones and determining how these hormonal changes influence the compensatory response to exercise is a crucial need for determining how exercise can be used most effectively to promote weight control.

1.3 Research Questions

1. Does aerobic exercise frequency, after a 12-week intervention, influence postprandial changes in plasma acylated ghrelin, leptin, GLP-1, and insulin concentrations?
2. Can identifying hormonal changes and their influence on compensatory responses to exercise determine which variables predict sufficient weight loss?

1.4 Hypothesis

1. Ghrelin concentrations will increase while leptin and GLP-1 concentrations will decrease in response to a meal to a greater extent when engaging in 6 weekly aerobic exercise sessions compared to 2 sessions after 12 weeks.
2. Changes in hunger hormones after 12 weeks of exercise will predict body fat loss, with changes in Ghrelin being negatively associated with body fat loss and Leptin, GLP-1, and insulin being positively associated with body fat loss.

CHAPTER 2. Literature Review

2.1 Introduction

America is among the countries with the most significant overweight and obesity rates, with rates continually rising [2, 3]. 70.9% of men and 61.9% of women are deemed overweight (Body Mass Index [BMI] 25.0-29.9 kg/m²) or obese (BMI ≥ 30.0 kg/m²), compared to 38% of men and 36.9% of women in all other countries [2, 3]. BMI is highly correlated with adiposity and the development of comorbidities such as cardiovascular disease, type 2 diabetes, fatty liver disease, and certain cancers [1, 5, 6, 18].

Adiposity begins with the amount of energy intake being more than the amount energy expended [5, 6]. Energy intake is complex and controlled by many different physiological, behavioral, psychological, and environmental factors [5, 7]. These factors contribute to the imbalance between energy intake and expenditure among overweight and obese individuals [2, 8]. Specific physiological factors include alterations in appetite-regulating hormones, posited to influence energy intake significantly [8, 9].

It is well-known that a diet-induced energy deficit can result in a negative energy balance and weight loss [1, 19]. Among overweight to obese individuals, diet-induced energy deficits are difficult to maintain due to changes in concentrations of appetite-regulating hormones functioning to increase sensations of appetite cues [1, 6, 19]. This makes it extremely difficult to maintain significant weight loss. Exercise training is another means for weight loss many individuals use, increasing energy expenditure to promote a negative energy balance (known as exercise training-induced energy deficit) [9-11, 16, 19-24]. Many acute/short- and long-term studies have investigated how an exercise training-induced energy deficit may influence these hormones, with many offering conflicting results [10-17, 21, 25-28]. Specific characteristics and behaviors such as sex, body adiposity, and diet may contribute to the varying effects exercise has on fasting- and postprandial concentrations of appetite-regulating hormones [10, 29-32].

Furthermore, the effects of different modes and frequencies of exercise on appetite-regulating hormone concentrations are not thoroughly understood, making it difficult for health care professionals to prescribe the most effective exercise training program for overweight to obese men and women [10, 12, 13, 15, 25, 28, 33]. The purpose of this review is to investigate factors that can influence fasting and postprandial concentrations of the appetite-regulating hormones, including the attributes of an exercise program.

2.2 Physiology of Hunger and Satiety Inducing Hormones

Appetite regulation is primarily driven by peptide hormone control, operating at the brain, gut, and peripheral regions [8, 9, 34, 35]. These appetite-regulating agents administer different inputs and signals from these regions that interact with various brain systems [8, 35]. This includes the brainstem that receives neuronal inputs from the digestive tract and the hypothalamus, which receives hormonal and nutritional signals from peripheral blood circulation [8, 9, 35]. These signals are received directly by neurons on the arcuate nucleus (ARC), a particular segment of the hypothalamus, through the blood-brain barrier [8, 9, 34, 35]. Together, these systems collect information about the body's nutrient status and respond accordingly by controlling sensations of hunger and satiety, influencing energy intake, and often playing a role in body weight regulation [8, 9, 34, 35].

2.2.1 Appetite-Regulating Neurons of The Hypothalamus

Within the ARC, there are two classes of neurons that run adjacent to one another: 1) the appetite-inhibiting neurons expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), and 2) the appetite-stimulating neurons expressing neuropeptide Y (NPY) and agouti-related peptide (AgRP) [18, 35-37]. Stimulation of the POMC-CART neurons will deactivate the hypothalamic feeding centers, decreasing appetite or feeding behavior [8, 36, 38]. Notably, POMC reduces appetite by releasing the neurotransmitter alpha-melanocyte-stimulating hormone (a-

MSH) [8, 36, 38]. A-MSH binds to the melanocortin-4 receptor (MC4-R) on the paraventricular nucleus (PVN) [8, 36, 38, 39]. In response, PVN projects the stimulus to other sites through the brain coordinating energy homeostasis [8, 30, 35]. This makes MC4-R the critical receptor for appetite control and energy homeostasis [8, 36, 38]. The other appetite-inhibiting neuron, CART, has been associated with sensory processing, with decreased expression observed in food deprivation [8, 36]. Activation of both POMC and CART is through the renowned anorexigenic hormone, leptin [40, 41].

2.2.2 Leptin

Leptin is a cytokine synthesized and released from adipocytes in response to changes in energy stores and systemic energy balance [8, 18, 40, 41]. The main action of leptin is to stimulate satiety while simultaneously inhibiting appetite [8, 18]. Leptin circulates partially bound to plasma proteins, with concentrations proportional to the degree of adiposity, and enters the ARC by diffusion [8, 18, 40]. The receptor of leptin associated with energy homeostasis, secretory organs' regulation, and innate and adaptive immunity is found in the hypothalamus and defined as Ob-Rb.[8, 18, 40-42] This receptor is a type I cytokine receptor and is encoded by the LEPR gene in humans [42]. Ob-Rb is present at multiple hypothalamus sites, such as the ARC and PVN [35, 40]. The expression of the Ob-Rb receptor is in many different forms [40]. These forms include the long-form, which is necessary for the action of leptin on appetite, and the short form, which plays a role in transporting leptin across the blood-brain barrier [40]. The Ob-Rb receptor plays a significant role in early obesity development when a lack of the receptor is expressed [40]. Leptin stimulates satiety is through POMC-CART activation upon binding to the leptin receptor located on the ARC [8, 40]. Leptin's additional role of attenuating appetite is through NPY and AgRP activation upon binding to NPY-G-protein-coupled receptors and melanocortin receptors located on ARC [8, 40]. Other leptin effects include increased insulin sensitivity through decreasing intracellular

lipid levels in skeletal muscle, liver, and pancreatic beta cells [41]. Since leptin's level of secretion depends on adiposity, individuals with obesity typically have greater leptin concentrations than lean counterparts [40, 41]. However, leptin resistance is often experienced in obesity, mediated by leptin signaling inhibition [40, 41]. Leptin resistance facilitates the sensation of hunger and leads to increased energy intake among individuals with obesity [8]. Normal regulation of leptin in neurons of the ARC not only stimulates POMC-CART activation but inhibits the appetite-stimulating neurons, NPY, and AgRP [8, 18, 40-42].

2.2.3 NPY and AgRP

Throughout the ARC to the PVN and other hypothalamic sites, NPY neurons' are expressed [36, 37]. NPY is one of the most abundant neuropeptides and most potent orexigenic factors [8]. These neurons are inhibited by leptin and insulin while stimulated by glucocorticoids and ghrelin [8, 36, 37]. The main physiological action of NPY is appetite stimulation through the NPY-G-protein-coupled receptors Y1 and Y5 (Y1R/Y5R) [8, 30, 36, 37]. Additionally, NPY represses the satiety stimulation effect of a-MSH by producing AgRP signaling proteins [36]. AgRP is a ligand of the melanocortin receptor subtypes MC3-R and MC4-R [8, 18, 30]. When AgRP binds, it represses a-MSH production by blocking its receptor MC1-R [8, 39]. Primarily, signal activation of both NPY and AgRP is through the well-known appetite stimulant ghrelin [8, 37].

2.2.4 Ghrelin

Ghrelin, or growth hormone (GH)-releasing peptide, is the single peripheral peptide known to increase appetite [8]. Ghrelin directly stimulates the expression of neurons NPY and AgRP in the ARC, consequently stimulating food intake [43]. Ghrelin also promotes food intake due to its antagonizing effect on leptin, as ghrelin and leptin compete for neuron interaction stimulating or inhibiting NPY [8]. Ghrelin is mainly produced in the stomach by the endocrine cells of the fundus' gastric mucosa [8, 9, 44].

Ghrelin is also an endogenous ligand for the growth hormone secretagogue-receptor type 1a (GHS-R1a) [8, 9, 44]. Several central nervous system (CNS) areas involved in energy intake regulation, such as the mesolimbic dopaminergic system, dorsal vagal complex, and the hypothalamic nuclei express GHS-R1a [8, 9, 44]. Besides appetite stimulation, ghrelin has multiple effects such as GH, acetylcholine (ACTH), cortisol, aldosterone, catecholamine, and prolactin secretion [8, 9, 44]. High ghrelin levels are typically observed in the fasted state, which falls following meals [45, 46]. Ghrelin levels are inversely correlated with adiposity and are slower postprandial decline among overweight or obese [8, 47, 48]. This slower postprandial drop in ghrelin impairs meal-induced satiety, predisposing individuals with greater adiposity to greater energy intake and potentially weight gain [45, 47, 48]. In contrast, peripheral peptides that are associated with satiety, in addition to leptin, include cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and insulin [8, 9, 18].

2.2.5 CCK

The satiety inducing peptide hormone CCK is found extensively in the brain and GI tract and was one of the first peptides discovered inside the gut in 1943 [49]. CCK plays numerous physiological and neurological roles such as mediating digestion in the small intestine through inhibiting gastric emptying, stimulating digestive enzyme release in the pancreas, and stimulating gall bladder contraction and sphincter of Oddi relaxation, which increases production and delivery of bile [8, 9, 18, 50, 51]. CCK also mediates satiety through acting on CCK receptors in the CNS [8, 51, 52]. CCK is produced and released by enteroendocrine cells in the mucosal lining of the duodenum and jejunum (I cell, IC), and neurons in the enteric nervous system (ENS) and brain [8, 9, 18, 50, 51]. The stimulation of CCK release is primarily by fatty acids (FA) or specific amino acids (AA) present in the chyme [8, 9, 18, 50, 51]. Other modes of CCK activation include monitor peptide, CCK-releasing protein, and acetylcholine [8, 9, 18, 50, 51].

Other means of CCK inhibition include somatostatin (growth hormone-inhibiting hormone), pancreatic peptide (PP), and trypsin (a pancreatic enzyme) [8, 9, 18, 50, 51]. There are many different forms of CCK; however, all forms bind to two distinct receptors: CCK-A and CCK-B [8, 9, 18, 50, 51]. CCK-A is primarily located on vagal afferent and enteric neurons in the pancreas with smaller amounts in the CNS and is mainly responsible for sensations of satiety and inhibiting food intake [51]. To activate CCK-A receptors, they require binding of sulfated tyrosine moiety of CCK-8 and CCK-33; these forms have a high affinity for the CCK-A receptor [50, 51]. CCK-B is primarily found in the CNS and does not affect food intake [50, 51]. Activation of CCK-B requires gastrin, de-sulfated CCK, and CCK-4 (a CCK fragment) binding to activate; these forms have a high affinity for the CCK-B receptor but low affinity for the CCK-A receptor [50, 51]. Intraperitoneally (IP) administered CCK can inhibit food intake by reducing meal size and duration [52]. However, since CCK's half-life is short (1-2 minutes), IP injection is most effective immediately before a meal [8, 52]. CCK concentrations gradually increase over 10-30 minutes after meal initiation due to specific nutrients in the gut, primarily fat and protein, and remain elevated for up to 5 hours [8]. In bodyweight regulation, CCK plays an important role and may act synergistically with leptin, whereas leptin potentiates the magnitude of feeding suppression signals produced by CCK [9, 51]. CCK-A deficiency can, therefore, increase the development of obesity due to decreasing the binding of CCK, resulting in decreased food reduction signals, leading to increased food intake and weight gain [8, 9, 49, 51].

2.2.6 PYY

PYY, a gut-derived hormone, is produced by the intestinal L cells of the ileum, colon, and rectum and secreted postprandially [8, 9, 18]. Postprandial concentrations of PYY are proportional to the meal macronutrient content, with higher levels observed after a high-fat meal than a high carbohydrate and protein meal [8]. Peripheral circulation

of PYY exists in two forms: PYY_{1-36} and PYY_{3-36}, with PYY_{3-36} as the peripherally active anorectic signal [8, 9, 18]. PYY_{3-36} is formed by cleavage of the N-terminal Tyr-Pro residues by dipeptidyl peptidase IV (DPP-IV) and binds to Y2 receptors (Y2R) to inhibit NPY neurons and stimulate POMC neurons [8, 9, 18]. The Y2R is a putative inhibitory pre-synaptic receptor and is part of the Y family of G-protein coupled receptors [8, 9, 18]. These receptors are highly expressed on the NPY neuron in the ARC but not on POMC neurons [9]. Binding of the Y2R agonist, PYY_{3-36}, to its receptors, Y2R, stimulates appetite inhibition by decreasing food intake sustained for 24-hrs [53, 54]. IP and intra-ARC (I-ARC) injection of PYY_{3-36} in obese and normal-weight individuals expresses these appetite inhibition effects [53, 55]. Administered PYY_{3-36} in the peritoneum and I-ARC can also reduce weight gain; however, PYY can also have appetite-stimulating effects [8, 9, 18, 53]. For instance, administered PYY_{3-36} in the intracerebroventricular vein (ICV) stimulates food intake by binding the Y1R and Y5R in the PVN [55]. Y1R and Y5R are also targeted by the orexigenic ARC NPY neurons, which increase appetite [8, 9, 18]. This hormone plays a significant role in appetite and weight regulation by reducing energy intake and body weight gain when injected through the IP and I-ARC; therefore, it is an essential appetite-regulating hormone to observe among obese and overweight individuals [56]. Obese individuals can develop PYY deficiency due to a lower endogenous PYY response after each meal than normal-weight individuals [8, 56]. PYY deficiency can alter appetite and weight gain regulation, thus reinforcing obesity [8, 56].

2.2.7 GLP-1

Another appetite-regulating peptide hormone that is 30 or 31 amino acids long and derived from posttranslational processing of proglucagon is known as GLP-1 [8, 9, 18, 30, 57-61]. Activation of the proglucagon's posttranslational process includes expression of the proglucagon gene, and transcription and cleavage of proglucagon

must occur [57-61]. Several organs express this gene, such as the alpha-cells (a-cells) of the pancreas, intestinal enteroendocrine L-cells of the gut (specialized cells of the GI tract/pancreas with endocrine function), and the caudal brainstem and hypothalamus within the brain [8, 9, 18, 30, 57-61]. Within the a-cells of the pancreas, proglucagon is cleaved and transcribed by site-specific prohormone convertase 2 (PC2), which generates the active glucagon, glicentin-related polypeptide (GRPP), intervening peptide 1 (IP1), and major proglucagon fragment (derived from GLP-1, IP2, and GLP-2; Figure 1) [57, 61]. Within the intestinal enteroendocrine L-cells of the intestine, primarily the jejunum/duodenum, the caudal brainstem, and hypothalamus, proglucagon is catalyzed by PC1/3 to form glicentin formed by GRPP, glucagon, and IP1 [57, 59, 61]. Additional products of processing glicentin include GRPP, oxyntomodulin (derived from glucagon/IP1), IP2, GLP-1, or GLP-2 [57, 59, 61]. Along with oxyntomodulin and other peptide hormones, GLP-1 is an incretin [59]. Incretins can enhance glucose-stimulated insulin secretion by decreasing blood glucose levels in a glucose-dependent manner [59]. GLP-1 is converted into two circulating bioactive forms, GLP_{17-36} amide and GLP_{17-37} [57, 61]. GLP_{17-36} accounts for about 20% of active GLP-1, whereas GLP_{17-37} is the most abundant form and accounts for about >80% [57, 61]. GLP_{11-37} is first catalyzed by endopeptidase to GLP_{17-37} [57, 61]. Next, GLP_{17-36} is amidated by the glycine terminal AA, which serves as a substrate for C-terminal arginine, producing the active GLP_{17-36} [57, 61]. After the bioactive forms are released, they are rapidly degraded by dipeptidyl peptidase (DPP)-4 to GLP19-36 or GLP19-37; thus, explaining why GLP-1 has a short half-life (1-2 minutes) in blood circulation [8, 57, 61]. GLP-1 has various physiological functions in the gut, brain, and pancreas [8, 9, 18]. GLP-1 in the gut inhibits gastric emptying, acid secretion, and motility, which collectively result in decreased appetite [8, 9, 18]. In the brain, GLP-1 has correlated with neurotrophic (neurogenesis) and neuroprotective (necrotic/apoptotic signaling and cell death reduction) effects [61].

Within regions of the brain such as the brainstem and hypothalamus, GLP-1 activates certain neurons in the ARC and PVN, the solitary tract's nucleus, and area postrema that lead to decreased appetite [61]. Looking at the pancreas, the most notable ability of GLP-1 is promoting insulin secretion through a glucose-dependent manner, inhibiting glucagon secretion, and replenishing beta-cell insulin stores during secretion [57, 61]. GLP-1 replenishes beta-cell insulin stores by promoting insulin gene transcription, mRNA stability, and mRNA biosynthesis [57, 61]. The binding of GLP-1 initiates these actions to its receptor, which is a G-protein coupled receptor [57, 61]. Many tissues such as pancreatic islet cells, lung, heart, kidney, stomach, intestine, pituitary, skin, vagus nerve, and certain CNS regions such as the brainstem and hypothalamus express the GLP-1 receptor (GLP-1R) [8]. Effects of ICV and IP administration of GLP-1R agonists (exenatide, lixisenatide, liraglutide) are consistently associated with decreased food intake and weight loss, whereas effects of ICV and IP administration of GLP-1R antagonists (NPY, exendin9-39) include increased food intake weight gain [57, 62]. Figure 1 below describes the physiological mechanisms of GLP-1 production.

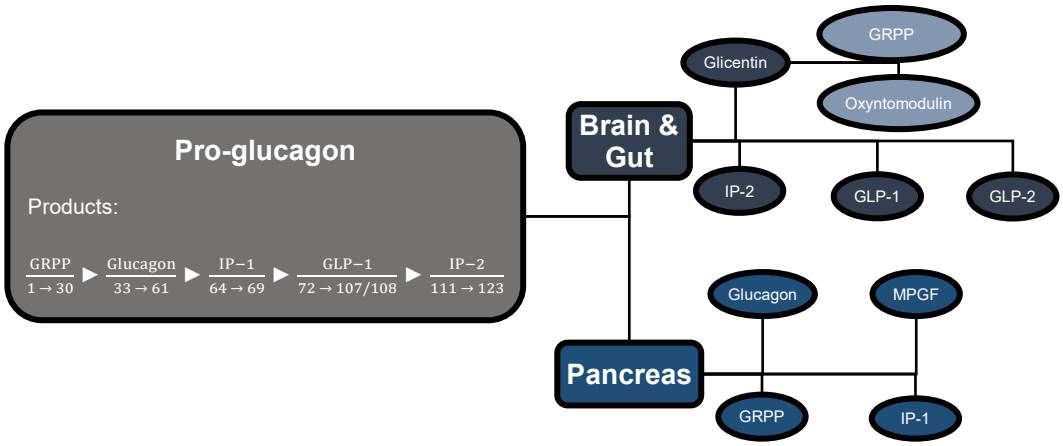

Figure 1. Products of pre-proglucagon cleavage Numbers (#→#) denote amino acid residues at which cleave occurs. GRPP; Glicentin-related pancreatic polypeptide, MPGF; Major pro-glucagon fragment.

2.2.8 Insulin

Lastly, another critical hormonal regulator of appetite and the first peptide hormone discovered is the anabolic hormone insulin [8, 9, 18, 30]. Insulin has various metabolism and appetite regulation roles; weight control; insulin also has a lipo-static role similar to leptin [8, 9]. Like leptin, circulating insulin levels are proportional to the degree of adiposity [8, 9]. Insulin has a half-life of approximately 4-6 minutes, and levels increase rapidly after meal consumption [57]. ICV administered insulin reduces food intake and body weight due to insulin receptors being highly concentrated and widely distributed in the brain [62]. These effects are initiated primarily by the ARC by inhibiting the NPY/AgRP neurons [59, 61, 62]. In circulation, insulin is produced and released by the endocrine pancreas' beta cells and degraded within one hour [59, 61, 62]. Blood circulation release of insulin can be stimulated by metabolic signals and vagal nerve stimulation and inhibited by specific metabolic signals, epinephrine, and somatostatin [9, 59, 61, 62]. The effects of insulin are activated from receptor binding, with the receptor found in the cell membrane [8, 9, 18, 30]. When insulin binds to the receptor, it triggers the B subunits' autophosphorylation, molecules inside the receptor, and subsequently, the phosphorylation of the insulin receptor substrates (IRS), which are proteins found inside the cell [8, 57, 59]. Expressed IRS in neurons with appetite-regulating and weight control effects consist of only two: IRS-1 and IRS-2 [8, 57, 59]. Increased food intake, adiposity, and plasma leptin levels have been demonstrated when neuron-specific disruption of the insulin receptor gene occurs [41]. Specifically, removing IRS-2 causes increased food intake and adiposity [41]. When describing the effects of insulin, interpretation is analogous to leptin [8, 9, 18, 41]. Through the adipo-insular axis, insulin can stimulate leptin synthesis and secretion from white adipose tissue [8, 9, 18, 41]. The relationship between insulin and leptin is typical in hypothalamic targets and common signal transduction pathways in the pancreas, muscles, and liver [8, 9, 18, 41].Table 1

shown below describes the physiological characteristics of the appetite-regulating hormones.

Table 1. Overview of the physiological mechanisms in correspondence to the appetite-regulating hormones.

Region	Hormone/ Peptide	Primary Production Site	Receptor(s)	Effect on Appetite	Other Action(s)
Hunger					
Brain	NPY	Medial ARC and other hypothalamic sites	Y1, Y5	Increase	Antagonizing POMC actions
Peripheral	Ghrelin	Stomach (endocrine cells of the gastric mucosa of the fundus)	GHS-R1a	Increase	Stimulates expression of NPY/AgRP, release of GH and other pituitary hormones, gastric motility, pancreatic polypeptide (PP) release
Satiety					
Brain	POMC/a-MSH	ARC	MC3-R, MC4-R	Decrease	Stimulates basal metabolic rate
Peripheral	CCK	I-cells of duodenum, jejunum; widespread CNS expression	CCK-A, CCK-B	Decrease	Stimulates pancreatic secretion, gall bladder contraction, intestinal motility. Inhibits gastric motility
Peripheral	PYY	L-cells of distal small/larger intestine; immunoreactivity in hypothalamus, medulla	Y2	Decrease	Inhibits gallbladder secretion, gut motility, pancreatic secretion
Peripheral	GLP-1	L-cells of distal small/large intestine; immunoreactivity in hypothalamus, dorsovagal complex, pituitary	GLP-1 receptor	Decrease	Promotes pancreatic B-cell growth. Inhibits glucagon release, gastric emptying, and secretion
Peripheral	Insulin	Beta cells of the endocrine pancreas	Insulin receptor	Decrease	Various roles in metabolism
Peripheral	Leptin	Adipose tissue	Leptin receptor (Ob-Rb)	Decrease	Stimulates POMC-CART, increase insulin sensitivity

2.3 Appetite-Related Hormones in The Development of Obesity

2.3.1 Heterogeneity of Fasting and Postprandial Concentrations of Appetite-Regulating Hormones

Many clinical trials investigate the effects exercise has on fasting and postprandial concentrations of appetite-regulating hormones [10, 12, 13, 27]. However, various findings are observed among these studies due to the heterogeneity in methodologies and outcome measures [10, 12]. For example, different sex, body adiposity, and diet are factors that can yield differentiating effects in appetite-regulating hormone concentrations in response to exercise [12]. Thus, considering differences in these variables is essential when concluding exercise for weight control interventions. The findings of many exercise for weight control studies that do not monitor sex, body adiposity, and diet differences are varied, limited, and call for further research to be conducted [10, 12, 13, 21, 25, 27, 28]. Inversely, studies that do monitor sex, body adiposity, and diet conclude equivocal findings of these characteristics and behaviors on appetite-regulating hormone responses to acute (after a single exercise bout) or chronic / long-terms exercise interventions [12]. To further understand the influence sex has on appetite responses to different types of exercise, recent studies that monitor these characteristics and behaviors will be examined and discussed.

2.3.2 Sex

Taking sex differences into account during exercise for weight loss interventions would minimize varied findings/results and improve understanding of the unknown mechanisms that influence appetite with exercise. In the physiology of appetite and energy intake, females and males have different activation and organization effects of reproductive hormones (androgens & estrogens) [63]. The relatively permanent effects of gonadal steroid hormones in early development or puberty are the organizational effects [63]. Activation effects are relatively reversible effects at other life stages and

require anatomic substrates in early development by sexually differentiated organizational processes [63]. These reproductive hormones can influence many mechanisms of appetite and energy intake [12, 63]. However, studies that analyze exercise-induced changes in appetite-regulating hormones generally feature mostly males participants [12]. Males in exercise and appetite research typically relate to cyclical changes in reproductive hormones, whereas different phases of the menstrual cycle in females influence the action of appetite-regulating hormones [64]. For example, energy intake, plasma GLP-1, and insulin are suppressed during the follicular phase, and total PYY concentrations are lower during the luteal phase of the menstrual cycle [64, 65]. Research on exercise and appetite has recently focused on appetite changes after exercise in females, suggesting that females compensate more for exercise-induced energy deficits over more extended periods to preserve more body adiposity than males [66].

Designated in Table 2, the purpose of this section is to discuss and consolidate recent findings of the modulating effects of sex on concentrations of appetite-regulating hormones with exercise-induced weight-loss interventions.

2.3.2.1 Acute Exercise

Comparisons of acute exercise-induced changes in appetite-regulating hormones between females and males demonstrate that both sexes have similar changes in appetite-stimulating responses [67-70]. It is essential to discuss that the female subjects completed all trials in the follicular phase of the menstrual cycle within these studies, which helped minimize the confounding effects on the measured appetite-regulating hormones [67-70]. Effects of a single bout of vigorous-intensity exercise (70% VO_2 peak) on the appetite-stimulating hormone, acylated ghrelin, was suppressed in females and males [67, 68, 71]. However, the effects of sex on the appetite-inhibiting hormones are less conclusive [68-71]. For example, Panissa et al. reported no effect of exercise on

PYY_{3-36}, while Hagobian et al. indicated that PYY_{3-36} concentrations were increased after exercise in only females [68, 71]. Hazell et al. also found elevations in total GLP-1 concentrations after moderate-intensity cycling (65% VO_2 peak) and sprint interval cycling in only females [69]. Hazell et al. also found that total GLP-1 concentrations were elevated after moderate-intensity cycling (65% VO_2 peak) and sprint interval cycling in only females [69]. However, Shamlan et al. demonstrated that total GLP-1 concentrations were not affected by high-intensity intermittent or continuous low-intensity cycling in females and males [70]. Due to the differentiating results in the literature, it is difficult to conclude whether sex affects appetite-suppressing hormones in acute exercise [67, 68, 70-72].

2.3.2.2 Chronic Exercise

Few studies have directly examined potential sex differences within the appetite-regulating hormones in response to chronic exercise [12]. Some report fasting leptin and insulin concentrations are significantly reduced after a 12-week exercise intervention in only females [73]. Similarly, after a four-day exercise intervention fasting leptin and insulin concentrations are reduced [74]. In contrast, more significant reductions in insulin and a greater elevation in acylated ghrelin were observed postprandially in overweight and obese females than males, although findings reported no differences in fasting leptin changes between females and males [74]. These studies' findings support the suggestion that changes in the appetite-regulating hormones in response to exercise-induced energy deficits are divergent in females compared to males [74]. However, due to the insufficient amount of conducted research that observes how sex influences the appetite-regulating hormones in response to chronic exercise, more exercise training intervention studies need to be conducted before making a decisive conclusion [12]. Furthermore, most studies utilize aerobic exercise training interventions [12]. Thus, the literature findings are restricted; therefore, conducting more research will investigate

potential sex differences in the appetite-regulating hormones with other exercise modalities that may differ in duration and intensity.

Table 2. Overview of articles that analyzed the modulating effects of sex on concentrations of appetite-regulating hormones with exercise.

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Alajmi et al. [67]	Experiment 1: N = 12, three 9-hr trials (control, exercise-induced [Ex-Def], food restriction-induced energy deficit [Food-Def]), identical energy deficits imposed in Ex-Def & Food-Def trials, compared appetite/energy intake/acylated ghrelin/PYY_{3-36} responses to an equivalent energy deficit induced by exercise or energy restriction Experiment 2: N = 20, Two 7-hr trials (Control & Exercise), 60 minutes of running performed at beginning of exercise trial, directly compared appetite/food intake/circulating acylated ghrelin responses to an exercise-induced energy deficit in men vs. women	Experiment 1: 90 minutes of running (~70% VO_2 max) Experiment 2: 60 minutes of running (~70% VO_2 max)	Experiment 1: Women, ~22.4 years, BMI ~22.0 Experiment 2: Men (aged ~22.6 years) & women (aged ~22.3 years), BMI ~22.4-23.1	Women exhibit compensatory appetite/gut hormone/food intake responses to acute energy restriction but no in response to acute bout of exercise; Men & women exhibit similar acylated ghrelin/PYY_{3-36} responses to exercise-induced energy deficits
Panissa et al. [71]	N = 20, compare the effects of exercise intensity on appetite control: relative energy intake/hunger scores/appetite-regulating hormones, completed 6 session (2 screening/4 experimental) separated by at least 72-hr and a maximum of 1-wk for men; Randomized crossover design	High-intensity intermittent all-out exercise (HIIE-A) for 60 x 8 seconds interspersed by 12 seconds of passive recovery/High-intensity intermittent exercise (HIIE) at 100% of maximal load attained in incremental test/Steady-state exercise at 60% of maximal load (matched by work done)/Control session	Men (n=11) & women (n=9), aged 27 ± 3 years, physically active	None of exercise protocols generated a compensatory increase in energy intake in men/women; Acylated ghrelin/hunger perception were more suppressed and cortisol/insulin were more elevated in the HIIE-A compared with the control; Regardless of sex, Appetite hormones did not have a major impact on acute energy intake
Hagobian et al. [68]	N = 21, find whether acute exercise suppresses relative energy intake in both men/women exposed to same relative exercise treatment, Rested for 60 minutes or exercised on a cycle ergometer (~70% VO_2 max) until 30% of total daily energy expenditure was expended; Counterbalanced/crossover design	Rested for 60 minutes or exercised on a cycle ergometer (~70% VO_2 max)	Men (n=11) & women (n=10), aged 21 ± 2 years, BMI 26 ± 4 (men)/ 24 ± 2 (women)	Regardless of sex acute exercise to suppress relative energy intake is effective
Hazell et al. [69]	N = 21, participated three sessions in a randomized crossover design: (1) MICT, 30-min cycling at 65% VO_2Peak; (2) SIT, 6 × 30 s "all-out" sprints with 4-min recovery periods; (3) control (CTRL; no exercise); Determine whether any sex difference in total PYY, GLP-1 or perceived hunger exists following MICT/SIT	Moderate-intensity continuous exercise (MICT)/sprint interval exercise (SIT)	Men & women (n=11), aged 28.6±5.9 (men)/30.5±7.9 (women) years, BMI 23.7±2.2 (men)/23.5±2.8 (women)	Total PYY/GLP-1 respond differently to exercise in males/females over 90 minutes following various exercise intensities

Table 2. (continued)

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Shamlan et al. [70]	N = 40, undertook either high-intensity intermittent cycling (HIIC) consisting of 8 repeated 60-second bouts of cycling at 95% $\dot{V}O_2$ peak or low-intensity continuous cycling (LICC), equivalent to 50% $\dot{V}O_2$ peak, matched for energy cost (~950 kJ) followed by 90 minutes of rest; Randomized crossover design	High-intensity intermittent cycling (HIIC)/low-intensity continuous cycling (LICC)	Men & women (n=19), aged 18-35 years, BMI 23.6 ± 3.6, recruited from the University of Surrey and wider community	High-intensity exercise, if energy matched, does not lead to greater appetite or energy intake, but may exert additional beneficial metabolic effects that may be more pronounced in males
Chronic Exercise				
Hickey et al. [73]	N = 18, determine the effect of aerobic exercise training on systemic leptin levels in humans, 12-wk exercise training period; Randomized crossover design	Aerobic exercise training (4 day/wk., 30-45 min/day)	Sedentary men & women (n=9), age 48.8±1.8 (men)/45.6±1.7 years (women), BMI 32.1±1.1 (men)/26.1±0.6 (women)	Women have higher circulating leptin concentrations despite lower fat mass and exercise training appears to have a greater effect on systemic leptin levels in females than in males
Hagobian et al. [74]	N = 18, sedentary men and women follow exercise training programs with ad libitum feeding, men lose body fat, but women do not; Purpose of this study was to evaluate whether this observation could be related to sex differences in the way energy-regulating hormones and appetite perception respond to exercise; Concentrations of hormones related to the regulation of energy intake/expenditure and perception of hunger/satiety were measured in three conditions: *1*) after a no-exercise day with subjects in energy balance, *2*) after 4 days of daily exercise with energy added back to the baseline diet to match the higher expenditure and maintain energy balance (BAL), and *3*) after 4 days of daily exercise without energy added to the baseline diet, so that subjects were in energy deficit (DEF); Counter-balanced/cross-over study design	Exercise bout was conducted on a treadmill (Life Fitness 9100, Schiller Park, IL) at a moderate intensity (50–65% of estimated $\dot{V}O_2$ Peak) until 30% of total daily energy expenditure was expended	Overweight/obese sedentary men & women (n=9), aged 26.8±11.8 (men)/23.3±8 (women), BMI 25.7±2.3 (men)/28.0±3.5 (women)	In women-exercise altered energy-regulating hormones in a direction expected to stimulate energy intake, regardless of energy status; In men-the response to exercise was abolished when energy balance was maintained

2.3.3 Body Adiposity

Even with the continuous rise of obesity today, observations of significantly varied whole-body adiposity are in individuals in westernized societies [75]. The wide variability in whole-body adiposity levels is associated with numerous factors that modulate energy intake/expenditure [12]. Current evidence suggests that body adiposity can influence appetite-regulating hormone concentrations after exercise [26, 48, 76, 77]. Studies have indicated that fasting and post-prandial changes of certain appetite-regulating hormones such as PYY, GLP-1, and acylated ghrelin are lowered and dampened as body fat increases [23, 78, 79]. Similarly, reports conclude that elevated leptin and insulin concentrations among overweight and obese populations studies [78, 80]. However, continuous evaluation of leptin and insulin can result in these hormones' resistance and ineffectiveness [12]. Many exercise-induced weight control interventions that measure appetite-regulating hormone concentrations have been conducted at varying BMI levels, thus increasing individual variability in the changes in these hormonal concentrations [12]. Since BMI is unable to differentiate between fat mass from fat-free mass and can lead to inaccurate descriptions of lean, overweight, or obese, further studies should alleviate this discrepancy by defining body adiposity with specific body fat percentages [12].

Identified in Table 3, the purpose of this section is to discuss and consolidate recent findings of the modulating effects of body adiposity on concentrations of appetite-regulating hormones with exercise-induced weight-loss interventions.

2.3.3.1 Acute Exercise

Studies have reported that among lean, overweight, and obese populations, acylated ghrelin decreases and increases in PYY and GLP-1 during and after acute aerobic exercise in both populations [13, 21, 81, 82]. For instance, Larsen and colleagues found that after performing resistance exercise, total PYY and total GLP-1 did not change in overweight males (Average BMI: 29.9 kg/m²), with similar findings in lean males (Average BMI: 23.7 kg/m²) [13, 21]. However, there are conflicting findings of the appetite-regulating hormone responses after different exercise intensities among lean, overweight, and obese subjects [12]. Two studies reported that neither moderate- nor high-intensity cycling altered circulating PYY concentrations in overweight/obese subjects, whereas a study conducted with lean subjects exhibited elevated PYY concentrations at greater exercise intensities [15, 17, 83, 84]. On the other hand, Unick et al. stated that overweight and obese females exhibited decreased GLP-1 concentrations 1-hr after a single bout of moderate-intensity walking [85]. Recently, Holliday and Blannin demonstrated opposing results among overweight/obese subjects in which GLP-1 was elevated 1-hr after low-volume sprint interval cycling [81].

These findings' variance could be due to the heterogeneity in methods and outcome measurements among these studies. Others have mitigated this variability by direct comparison of subjects with directly comparing the same protocol [26, 86, 87]. For example, Ueda et al. observed that total PYY and GLP_{7-36} concentrations exhibited similar elevations up to 1-hr after moderate-intensity exercise in both lean (BMI: 19.1-24.7 kg/m²) and overweight (BMI: 26.0-34.6 kg/m²) subjects [87]. Others have demonstrated overweight/obese subjects (BMI: 25.3-35.4 kg/m²) exhibit more outstanding total GLP-1 elevations after 60 minutes of moderate-intensity treadmill exercise (59% VO_2 peak), while the lean (BMI: 19.6-24.5 kg/m²) group exhibited more significant elevations in exercise-induced total PYY concentration [26]. Regarding

acylated ghrelin, reports concluded the opposite, such as no modifications of acylated ghrelin concentrations in either overweight/obese or lean subjects after exercise were found [26]. Although studies that involve exercise intensities larger than 60% VO_2 Peak, opposing results were found in which acylated ghrelin was suppressed [10, 11, 88, 89]. Even with inconsistent results among the given literature, the collective evidence suggests that lean and overweight/obese individuals exhibit similar acute exercise-induced changes in energy intake [12]. When conducting future studies, inclusions should explain the inconsistencies in appetite-regulating hormones with varying body adiposity levels regarding body adiposities that influence appetite-regulating hormones.

2.3.3.2 Chronic Exercise

Most recent exercise for weight control studies that analyze body adiposity's influence on appetite-regulating hormones are primarily conducted among overweight/obese populations and conclude that exercise training increases fasting hunger and postprandial satiety [15, 90]. Regarding the appetite-regulating hormones, decreases in leptin concentrations and increases in GLP-1 concentrations have been observed after four weeks of moderate-intensity cycling (55% VO_2 Peak) in sedentary overweight males (Average BMI: 25.6 kg/m²) [24]. Similarly, Pil-Byung et al. observed decreases in leptin and total ghrelin concentrations after 8-weeks of combined resistance/aerobic training in sedentary individuals (BMI: 25.5 kg/m²) [91]. Both studies reported lower body weight and abdominal fat mass in response to exercise, which could mediate post-training changes in the appetite-regulating hormones [24, 91]. These findings suggest that individuals with more extensive pre-training adiposity exhibit more significant changes in appetite-regulating hormones, which are proportional to reductions in body fat post-intervention [24, 91]. A 12-week aerobic exercise intervention study conducted by Gibbons and colleagues supports these findings [92]. After the exercise intervention, in subjects who lost more weight, more massive elevated postprandial rises

in GLP-1 and total PYY concentrations, with more massive suppression in acylated ghrelin concentrations, were reported [15]. From a 12-weeks of high-intensity interval training intervention, similar findings such as increases in fasting acylated ghrelin were more significant in subjects that exhibited more extensive weight loss; however, this relationship in PYY_{3-36}, or GLP-1 concentrations were not found [15]. With decreased bodyweight after aerobic exercise training, additional findings of acylated ghrelin, PYY_{3-36}, and GLP-1 reported no change in fasting or postprandial concentrations [16, 33, 93]. Decreases in body fat also do not correspond to changes in acylated ghrelin and PYY concentrations after resistance exercise training in overweight and obese males [33].

Table 3. Overview of articles that analyzed the modulating effects of body adiposity on concentrations of appetite-regulating hormones with exercise.

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Larsen et al. [13]	N = 12; Completed four conditions in random order; Perceived appetite/appetite-related peptides/metabolites were assessed before/up to 2-hr post-condition (0P, 30P, 60P, 90P, 120P); Randomized/counter-balanced study design	Completed four conditions in a random order: 1) non-exercise control (CON) (50 min seated rest); 2) AE (50 min cycling; 75% VO_2Peak); 3) SE (10 × 8 leg extensions; 75% 1RM); and 4) CE (50% SE + 50% AE)	Sedentary overweight males (n=12); aged 48 ± 5 years; BMI: 29.9 ± 1.9	AE/SE/CE each have own distinct effects on circulating appetite-related peptides/metabolites; Despite differential exercise-induced hormone responses, exercise mode appears to have little effect on perceived appetite compared with a resting control in this population
Balaguera-Cortes et al. [21]	N = 10; completed 3 trials in a counter-balanced design; study investigated the effect of an acute bout of resistance exercise, compared with aerobic exercise, on subsequent energy intake/appetite-regulating hormone	3 trials: (1)45 min of resistance exercise (RES; free and machine weights), (2) aerobic exercise (AER; running), (3) or a resting control trial (CON)	Healthy active males (n=10); aged 21.3 ± 1.4 years; BMI: 23.7 ± 2.0	Differential response of appetite-regulating hormones to AER/RES does not appear to influence energy intake in the post-exercise meal
Sim et al. [84]	N =17; completed four 30-min experimental conditions using a randomized counter-balanced design; examine the acute effects of high-intensity intermittent exercise (HIIE) on energy intake, perceptions of appetite/appetite-related hormones in sedentary, overweight men	Four Conditions: (1) CON: resting control, (2) MC: continuous moderate-intensity exercise (60% VO_2Peak, (3) HI: high-intensity intermittent exercise (alternating 60 s at 100% VO_2Peak and 240 s at 50% VO_2Peak), (4) VHI: very-high-intensity intermittent exercise (alternating 15 s at 170% VO_2Peak and 60 s at 32% VO_2 Peak)	Sedentary overweight males (n=17), aged 30 ± 8 years, BMI 27.7 ± 1.6,	High-intensity intermittent exercise suppresses subsequent ad-libitum energy intake in overweight inactive men

Table 3. (continued)

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Martins et al. [17]	N = 12; assigned to the control, MICC, HIIC, and S-HIIC conditions, 1-wk apart, in a counter-balanced order; aim of the study was to compare the effects of acute isocaloric bouts (250 kcal) of high-intensity intermittent cycling (HIIC)/moderate-intensity continuous cycling (MICC)/short-duration HIIC (S-HIIC) (125 kcal)/a resting control condition on the appetite hormone responses/subjective feelings of appetite/energy intake (EI)/food reward in overweight/obese individuals	Four conditions: (1) high-intensity intermittent cycling (HIIC), (2) moderate-intensity continuous cycling (MICC), (3) short-duration HIIC (S-HIIC), (4) and a resting control condition; Exercise was performed 1-hr after a standard breakfast	Sedentary overweight/obese males & females (n=7), aged 33.4 ± 10.0 years, BMI 32.3 ± 2.7	In overweight/obese individuals, isocaloric bouts of moderate- or high-intensity exercise lead to a similar appetite response
Deighton et al. [83]	N = 12; completed three 8-hr trials (control), steady-state exercise (SSE), high-intensity intermittent exercise (HIIE)) separated by 1 week; Counter-balanced Latin square design	60 minutes of 3 different exercise trials: (1) control, (2) steady-state exercise (SSE), (3) high-intensity intermittent exercise (HIIE)	Healthy normal weight males (n=12), aged 22 ± 3 years, BMI 23.7 ± 3.0	Acute bout of energy-matched continuous exercise/HIIE were equally effective at inducing an energy deficit without stimulating compensatory increases in appetite
Unick et al. [85]	N = 19; underwent two experimental testing sessions in a counter-balanced order: (1) exercise and (2) rest; study examined the acute effect of a bout of walking on hunger/ energy intake/appetite-regulating hormones	Two trials: (1) walking at a moderate intensity for approximately 40 minutes (2) or rested for a similar duration	Sedentary overweight/obese females (n=19), aged 18-45 years, BMI 25.0-39.9	Hunger/energy intake were unaltered by a bout of walking suggesting that overweight/obese individuals do not acutely compensate for the energy cost of the exercise bout through increased caloric consumption
Holliday & Blannin [81]	N = 8; completed resting (REST)/exercise (EX) trials in a counter-balanced order; Counter-balanced/crossover study design	Exercise consisted of 4 × 30 s “flat-out” cycling on an ergometer (adapted Wingate test)	Active overweight males & females (n=4), aged 34 ± 12 years, BMI 27.7 ± 1.7	Little as 4 × 30 s of “flat-out” cycling was sufficient to elicit a transient suppression of appetite/an enduring suppression of plasma acylated ghrelin; food intake 2-h post-exercise was unaffected

Table 3. (continued)

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Ueda et al. [87]	N = 14; examined whether changes in gut hormone levels due to a single bout of aerobic exercise differ between obese young males/normal controls; attempted to determine the involvement of hormonal changes during exercise in the regulation of energy balance (EB); Randomized crossover design	Two trials: (1) constant cycling exercise at 50% VO_2Peak (2) or rest for 60 min	Overweight/obese & normal weight males (n=7), middle-aged	Findings suggest that short-term EB during a single exercise session might be regulated not by increased amounts of these gut hormones
Douglas et al. [26]	N = 47; study compared the acute effects of moderate-intensity exercise on appetite/energy intake/appetite-regulatory hormones in lean and overweight/obese individuals; completed two, 8-hr trials; Randomized crossover design	Two trials: (1/2) 60 minutes treadmill exercise (59% VO_2Peak) at 0-1-hr and rested after	healthy lean (n=22, 11 females; aged 37.5 (15.2) years; BMI 22.4 (1.5) and overweight/obese (n=25, 11 females; 45.0 (12.4) years, BMI 29.2 (2.9)	Acute moderate-intensity exercise transiently suppressed appetite/increased PYY/GLP-1 in the hours after exercise without stimulating compensatory changes in appetite in lean or overweight/obese individuals
Chronic Exercise				
Morishima et al. [24]	N = 22; conducted to determine change in regional fat accumulation and appetite-related hormonal response following hypoxic training; subjects underwent hypoxic (n = 9, HYPO, FiO(2) = 15%) or normoxic training (n = 11, NOR, FiO(2) = 20·9%) during a 4-week period (3 days per week); Randomized crossover design	4-week training at 55% of maximal oxygen uptake (VO_2Peak) for each condition	Healthy sedentary males 33 ± 2 years; BMI 25.6 ± 0.8	Hypoxic training for 4 weeks resulted in greater improvement in glucose tolerance without loss of whole-body fat mass, abdominal fat area or IMCL; Hypoxic training did not have synergistic effect on the regulation of appetite-related hormones
Pil-Byung et al. [91]	N =30; investigated the effects of an exercise program on appetite-regulating hormones, inflammatory mediators, lipid profiles, and body composition; Randomly assigned to two groups (exercise group, EG, N.=15 and control group, CG, N.=15)	-	Healthy sedentary males	Demonstrated the beneficial effects of an exercise program by altering appetite-regulating hormones, decreasing inflammatory factors, and improving lipid profiles and body composition in healthy young me

Table 3. (continued)

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Chronic Exercise				
Gibbons et al. [92]	N = 32; examined the role of postprandial peptide response in compensatory eating during 12 weeks of aerobic exercise and in response to high-fat, low-carbohydrate (HFLC) and low-fat, high-carbohydrate (LFHC) meals; Randomized crossover design	16 completed 12 weeks of aerobic exercise and 16 non-exercising control subjects were matched for age and body mass index	Overweight/obese & normal weight males (n=16); age 18-55 years, BMI 27-34	No impact on postprandial peptide release was found after 12 weeks of aerobic exercise; Responders to exercise-induced weight loss showed greater suppression of acylated ghrelin and greater release of GLP-1 and total PYY at baseline
Martins et al. [17]	N = 46; Aim of this study was to determine the effect of 12-wk of isocaloric programs of moderate-intensity continuous training (MICT), high-intensity interval training (HIIT), or short-duration HIIT on subjective feelings of appetite, appetite-related hormones, and reward value of food; Randomized crossover design	three training groups: (1) MICT (n = 14), (2) HIIT (n = 16), (3) or short-duration HIIT (n = 16); three times per week	Sedentary overweight/obese males & females (n=30), age of 34.4 ± 8.8 years; BMI 33.3 ± 2	Study suggests that chronic HIIT has no independent effect on appetite or food reward when compared with an isocaloric program of MICT in obese individuals
Guelfi et al. [33]	N = 33; Investigate the effect of 12 weeks of aerobic (AER) compared with resistance training (RES) on perceived hunger and fullness, together with appetite-related hormones in both the fasted state and postprandially; Randomized crossover design	AER and RES completed 12 weeks of training (3 sessions per week), while CON continued their sedentary routine	Sedentary overweight/obese males; aged 49 ± 7 years; BMI 30.8 ± 4.2	Aerobic exercise training is associated with an increase in satiety, while an equivalent period of resistance training is not

2.3.4 Diet

Diet is the pre-existing eating patterns/habits observed in an individual with varying macronutrient intakes [32]. Regarding macronutrients within a diet, the amount and combination of protein, carbohydrate, and fat can influence appetite-regulating hormone concentrations, thus influencing energy intake [94]. For instance, more significant increases of GLP-1 and PYY concentrations have been observed in males with high-protein intakes compared to both high-carbohydrate or high-fat intakes [54, 95]. This suggests that a high-protein diet can increase sensations of satiety and potentially lead to greater weight loss by reducing energy intake. Tischmann et al. supported this relationship between protein and satiety by comparing diets with different macronutrient intakes in which a high-protein/moderate-carbohydrate diet demonstrated greater elevations in PYY than the moderate-protein/high-carbohydrate diet [94]. In contrast, others indicate that a high-carbohydrate/fat diet had greater increases in GLP-1 than a high-protein diet [20]. These studies exhibit the influence of the diet's macronutrient composition on appetite-regulating hormone mediation; however, further investigations are required to determine whether diet alterations in exercise training interventions can further promote or maintain significant weight loss.

The studies that examine the influence of exercise-induced for weight loss interventions on diet and the effect they have on the concentrations of appetite-regulating hormones are designated in Table 4.

2.3.4.1 Acute Exercise

Recent literature suggests that different exercise types can alter diet; thus, altering appetite-regulating hormone concentration [14, 96]. Larson-Meyer observed increases in protein and fat intake and unchanged acylated ghrelin after 60 minutes of walking (70% VO_2 peak), whereas after 60 minutes of running (70% VO_2 peak), macronutrient intake was unchanged and acylated ghrelin was increased [14]. Similarly, Finlayson et al. demonstrated that after 50 minutes of vigorous-intensity cycling (70% VO_2 peak), subjects had a greater preference for energy-dense foods [96]. Conversely, Jokisch and colleagues found that meal macronutrient intake did not differ after exercise ≥150 min/week or ≤60 min/week, whereas Charlot and Chapelot exhibited after 60 minutes of exercise, fat and protein intake was increased [97, 98].

2.3.4.2 Chronic Exercise

An exercise training intervention and its effect on energy and macronutrient intakes and the appetite-regulating hormones are difficult to explain since most exercise training studies recruit sedentary subjects at baseline [12]. Nevertheless, measured fasting- and postprandial appetite and energy intake in subjects is typically observed in cross-sectional studies [99, 100]. Van Walleghen and colleagues demonstrated that exercise training subjects had greater energy and protein intake than the sedentary subjects [100]. Regarding studies investigating the effect of exercise training interventions on appetite-regulating hormones, the amount of literature is low [12]. However, one study found that fasting acylated ghrelin and GLP-1 concentrations were elevated in the exercise training group compared to the sedentary group, whereas total PYY was not significantly different between both groups [99]. This indicates that increased exercise training duration can increase energy compensation through manipulating appetite-regulating hormone mediation, thus reducing the promotion/maintenance of weight loss.

Table 4. Overview of articles that analyzed the modulating effects of diet on concentrations of appetite-regulating hormones with exercise.

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Larson-Meyer et al. [14]	N = 19, Plasma concentrations of the orexigenic peptide ghrelin/anorexigenic peptides PYY/GLP-1/appetite ratings were measured at 30 min interval for 120 min, followed by a free-choice meal Counter-balanced cross-over study design Purpose of this study was to assess the effect of a 60-minute bout of exercise on circulating concentrations ghrelin/PYY/GLP-1; appetite/*ad libitum* food intake among women	60 minutes of running/60 minutes of walking	Healthy active women (runners = 9), aged 18-40 years, BMI 19.8-22.1	Exercise-induced alterations in appetite are likely driven by complex changes in appetite-regulating hormones rather than change in a single gut peptide
Finlayson et al. [96]	N = 24, designed to examine hedonic/homeostatic mechanisms involved in the acute effects of exercise on food intake, conformed to a within-subjects design consisting of two counterbalanced conditions separated by approximately one week	Two conditions were (1) moderate-intensity exercise (Ex) which involved stationary cycling at approximately 70% maximum heart rate for 50 min, and (2) 50 min of no exercise (NEx)	Healthy females, aged 18-40 years, BMI 20-25, staff/student population of the University of Leeds	Exercise-induced changes in the hedonic response to food could be an important consideration in the efficacy of using exercise to lose weight; An enhanced implicit wanting for food after exercise may help to explain why some people overcompensate during acute eating episodes; Individuals could be resistant to the beneficial effects of exercise due to a predisposition to compensate for exercise-induced energy expenditure as a result of implicit changes in food preferences

Table 4. (continued)

Source	Study Details	Type of Exercise (Mode/Intensity)	Study Population	Key Findings
Acute Exercise				
Charlot & Chapelot [98]	N = 18, assessed role of 'fatness/fitness' in inter-individual variability, within-subject design/subjects separated into two groups according to their body fatness/fitness status/completing in random order the two following test conditions: (1) 60 min of exercise (EX)/(2) 60 min of rest (RT)	After 5 min warm-up period at 75 W, the workload was progressively increased over a 10 min period until the subjects reached 70 % of their VO_2Peak, intensity was then maintained over 45 min, continuous gas exchange permitted measurement of EE/constant adjustment of the workload so that exercise was maintained at the desired intensity	Non-obese males, aged 18-25 years, recruited through board advertisements in the Paris 13 University area (Paris, France)	Energy cost of an aerobic exercise session was partially compensated over the next 24-hr independently of the fatness/fitness status, but high-fat/low-fit individuals compensated more specifically on fats
Chronic Exercise				
Van Walleghen et al. [100]	N = 54, On two occasions, young active (n = 15), young sedentary (n = 14), older active (n = 14) and older sedentary (n = 11) subjects consumed either a high-energy yogurt preload beverage (YP: 500 ml, 1988 kJ, men; 375 ml, 1507 kJ, women), or no preload (NP), 30 min before an ad libitum test meal,	Not permitted to exercise	Healthy non-obese young physically active (aged 21–35 years) and sedentary/older physically active (aged 60–80 years) and sedentary adults	Acute EI regulation is impaired in older adults, which is not attenuated by physical activity status; EI regulation over the course of a day is more accurate in active vs sedentary adults, which may facilitate long-term energy balance
Lund et al. [99]	N = 20, aim of this study was to assess and compare gut hormone response and satiety changes after a liquid meal intake in young, healthy trained (T)/ untrained (UT) males Cross sectional in design and a prospective intervention study	T group was regular aerobic exercise performers doing long distance running/bicycling or triathlon ([three exercise bouts a week) during several years with a VO_2Peak [60 ml - min-1 kg-1 body weight UT group with a sedentary lifestyle, did not perform any aerobic/resistance exercise, during at least the last 6 months and a VO_2Peak\50 ml min-1 kg-1 body weight	Health normal weight males (n=20), aged 25±1 year, BMI ~22±1, recruited through notices posted on the Copenhagen University bulletin boards/in student magazines	Satiety measures did not differ between groups throughout the test; Possible that in aerobically T subjects, lower GIP release is partly responsible for a lower postprandial incretin stimulated insulin secretion

2.3.5 Types of Exercise Training

Several exercise-induced weight loss intervention studies support the correlations between exercise training with appetite-regulating hormone regulation [10, 12, 13, 16, 21, 25, 27, 28]. However, these studies' methodology and outcome measurements are widely diverse, making it difficult to determine the most efficient type of exercise that should be applied to increase the promotion/maintenance of weight loss [12]. The type of exercise in exercise training interventions are shaped by two factors: mode and frequency [12, 13]. The exercise mode is typically described as either aerobic or anaerobic, whereas exercise frequency is defined as the number of times the exercise is performed per week [16]. Various findings indicate whether aerobic/anaerobic exercise or a specific exercise frequency will differentially influence changes in appetite-regulating hormone concentrations [12, 16]. Recent studies that monitor these differentiating types of exercise will be further investigated to help understand the discrepancies in the literature [10, 12, 16].

The purpose of this section is to evaluate recent studies that observe the effect of exercise mode and frequency on the appetite-regulating hormones designate in Table 5.

2.3.5.1 Mode

It is suggested that exercise mode has no differing effects on energy intake. However, aerobic and anaerobic exercise have been demonstrated to have distinct and specific appetite-regulating responses [10, 13]. Larsen et al. found differing exercise-induced hormone responses in different exercise modes exhibited minimal effects on perceived appetite [13]. However, further investigation is considered due to the absence of total energy expenditure measurements and short study durations [13]. Cadieux et al. conducted a study that evaluated these parameters and found similar findings in which varying exercise modes exhibited no differences in energy intake [25].

2.3.5.2 Frequency

Dorling et al. elaborate on how the number of days per week an individual performs exercise could play a vital role in manipulating the appetite-regulating hormones [12]. Guelfi et al. found negligible differences after a short or long duration of exercise [33]. Recent literature on the effect of exercise frequency on the appetite-regulating hormones is scarce [12]. Two studies found that after a short and long duration of exercise training, the hormone concentrations of PYY, GLP-1, and PYY increased; however, there was no significant difference in the amount these hormones increased in either durations [13, 15]. Due to the limited amount of literature, the effect of the frequency of exercise on the appetite-regulating hormones is another parameter that should be further investigated [12].

Table 5. Overview of articles that analyzed the modulating effects of exercise mode and frequency on concentrations of appetite-regulating hormones.

Source	Study Details	Methods Compared	Study Population	Key Findings
Mode				
Larsen et al. [13]	N = 12; Completed four conditions in random order; Perceived appetite/appetite-related peptides/metabolites were assessed before/up to 2-hr post-condition (0P, 30P, 60P, 90P, 120P); Randomized/counter-balanced study design	Completed four conditions in a random order: 1) non-exercise control (CON) (50 min seated rest); 2) AE (50 min cycling; 75% VO_2Peak); 3) SE (10 × 8 leg extensions; 75% 1RM); and 4) CE (50% SE + 50% AE)	Sedentary overweight males (n=12); aged 48 ± 5 years; BMI: 29.9 ± 1.9	AE/SE/CE each have own distinct
Broom et al. [10]	N = 11; Completed three exercise trials with different conditions; Ratings of hunger and plasma concentrations of acylated ghrelin and PYY were measured and compared throughout the study; Purpose was to find the effects that resistance exercise has on appetite; Randomized crossover design	Three, 8-hr trials: 1) Resistance exercise: 90-min free weightlifting session followed by 6.5-hr rest period; 2) Aerobic exercise: 60-min run followed by 7-hr rest period; 3) Control: 8-hr rest	Healthy male students (n=11); aged 21.1 ± 0.3 years; BMI: 23.1 ± 0.4; maximum oxygen uptake: 62.1 ± 1.8 $ml \cdot kg^{-1} \cdot min^{-1}$	PYY concentrations were greater with the aerobic exercise trial than the other trials; Could indicate ghrelin and PYY may regulate appetite during and after exercise
Cadieux et al. [25]	N = 16; Objective was to evaluate the effects of exercise modality on energy intake (EI), total energy expenditure (TEE), non-exercise activity thermogenesis (NEAT), and post-exercise energy compensation (PEEC) measured acutely, as well as for 10-hr and 34-hr following exercise; Randomized crossover design	Three randomized crossover sessions: 1) Resistance (Training protocol; 70% VO_2Peak): Performed until the energy cost of exercise (ExEE) was reached; 2) Aerobic (Treadmill; 70% VO_2Peak): Performed until the target ExEE was reached; 3) Control: Had to remain seated during the 1-hr session and were only allowed to read	Healthy sedentary males (n=8) and females (n=8); aged 21.9 ± 2.6 years; BMI: 22.8 ± 1.8; maximum oxygen uptake (VO_2Peak): 53.0 ± 8.6 $ml \cdot kg^{-1} \cdot min^{-1}$	No differences in EI between modes of exercise, as well as 10-hr and 34-hr following exercise; Modality by sex interaction was found for acute EI (men ate more after the resistance session than the aerobic session, while women showed no difference); No differences found 10-hr and 34-hr post-exercise in TEE, NEAT and PEEC; Positive correlation found between both modalities across subjects for PEEC ($r = 0.897$; $P < 0.01$)

Table 5. (continued)

Source	Study Details	Methods Compared	Study Population	Key Findings
Frequency				
Guelfi et al. [33]	N = 33; Investigate the effect of 12 weeks of aerobic (AER) compared with resistance training (RES) on perceived hunger and fullness, together with appetite-related hormones in both the fasted state and postprandially; Randomized crossover design	AER and RES completed 12 weeks of training (3 sessions per week), while CON continued their sedentary routine	Sedentary overweight/obese males; aged 49 ± 7 years; BMI 30.8 ± 4.2	Aerobic exercise training is associated with an increase in satiety, while an equivalent period of resistance training is not
Larsen et al. [13]	N = 12; Completed four conditions in random order; Perceived appetite/appetite-related peptides/metabolites were assessed before/up to 2-hr post-condition (0P, 30P, 60P, 90P, 120P); Randomized/counter-balanced study design	Completed four conditions in a random order: 1) non-exercise control (CON) (50 min seated rest); 2) AE (50 min cycling; 75% VO_2Peak); 3) SE (10 × 8 leg extensions; 75% 1RM); and 4) CE (50% SE + 50% AE)	Sedentary overweight males (n=12); aged 48 ± 5 years; BMI: 29.9 ± 1.9	AE/SE/CE each have own distinct
Martins et al. [17]	N = 46; Aim of this study was to determine the effect of 12-wk of isocaloric programs of moderate-intensity continuous training (MICT), high-intensity interval training (HIIT), or short-duration HIIT on subjective feelings of appetite, appetite-related hormones, and reward value of food; Randomized crossover design	three training groups: (1) MICT (n = 14), (2) HIIT (n = 16), (3) or short-duration HIIT (n = 16); three times per week	Sedentary overweight/obese males & females (n=30), age of 34.4 ± 8.8 years; BMI 33.3 ± 2	Suggested that chronic HIIT has no independent effect on appetite or food reward when compared with an isocaloric program of MICT in obese individuals

2.4 Conclusion

Understanding the effect of sex, body adiposity, diet, and exercise type differences on appetite-regulating hormones with exercise training provides aid in the future direction literature should take. In recent literature, it is difficult to distinguish all the potential factors that modulate the appetite-regulating hormones in exercise training interventions due to the heterogeneity in methodologies and outcome measurements [12]. Although it appears that sex, body adiposity, and diet can influence concentrations of the appetite-regulating hormones to some degree, whereas exercise mode and frequency do not have different effects on these hormones. Further investigation into these factors is crucial for the development of future exercise training for weight control interventions. This information can be used by health care professionals to provide the most accurate exercise training recommendations that give the best results among overweight and obese populations.

CHAPTER 3. Materials and Methods

3.1 Research Design

The study was a randomized, controlled trial that included a 12-week exercise intervention with exercise frequencies of either six sessions (days) per week, two sessions per week, or a sedentary control group (no exercise), blocked by sex. Concentrations of ghrelin, leptin, glucagon-like peptide 1 (GLP-1), and insulin were assessed before (fasting, minute 0) and after a standardized meal at minute 15, 30, 45, 60, 90, 120, 150, and 180 at baseline and after the 12-week exercise intervention (post). Regarding exercise treatments, subjects were directed to only aerobic exercise (walking, running, biking, treadmill, elliptical, or stationary bike). A Polar A-300 heart rate monitor (watch and chest-/waist-strap) had to be worn during exercise, with subjects reporting back to the lab weekly to download and record each exercise session. Weekly meetings allowed to monitor adherence to the prescribed amount of exercise (2- or 6-days per week) and evaluate exercise-induced energy expenditure.

3.1.1 Recruitment

Recruitment occurred in and around Lexington, Kentucky, beginning in the winter of 2018 and ending in the spring of 2019. The inclusion criteria included BMI between 25 to 35 kg/m^2, 18 to 40 years of age, no physical limitations or major health problems, and not pregnant or planning a pregnancy in the next six months. The exclusion criteria included dieting over the past three months, tobacco use, taking metabolic altering medications, regularly exercising in the last six months, and any medical condition preventing safe exercise. The subjects collected had a BMI ranging from 25 to 35 kg/m^2, were weight-stable (not lost or gained 5% of their current body weight in the last six months), sedentary (not engaging in exercise), free of any metabolic or cardiovascular disease, not pregnant or nursing, and not participating in a weight loss diet or taking any appetite-regulating medications.

3.1.2 Subjects

A total of 53 participants volunteered and were randomized into one of three groups. Of these, 44 participants completed the study (32 women), with six (four women) withdrawing for personal reasons, and two female participants were excluded for noncompliance. Six individuals (3 females) did not have valid data for the hormonal mediators of hunger (processing or equipment error). Thus, 37 subjects (29 females) completed the 12-week intervention and were included in the analyses. All subjects had a body mass index (BMI) ranging from 25-35 kg/m^2, were weight-stable (not lost or gained 5% of their current body weight in the last six months), sedentary (not engaging in exercise), free of any metabolic or cardiovascular disease, not pregnant or nursing, and not participating in a weight loss diet or taking any appetite-regulating medications. The study was approved by the University of Kentucky Institutional Review Board and is registered with Clinicaltrials.gov identifier: NCT03413826.

3.1.3 Procedures

Subjects provided their written informed consent and were screened of eligibility criteria at an initial screening and consent visit. Screening of eligibility criteria included completing a health history and physical activity readiness questionnaire (PARQ), the Preference for and Tolerance of the Intensity of Exercise Questionnaire (PRETIE-Q), and an online survey of their weight loss history. Physical activity was objectively assessed for seven days before completing the baseline testing by an ActiGraph accelerometer that was provided and worn by each participant. During subsequent visits before and after the exercise intervention, the energy expenditure rate, resting energy expenditure (REE), body composition, and hormonal response to a standardized breakfast meal were obtained.

3.1.4 Exercise Intervention

A Polar A-300 heart rate monitor (watch and chest-/waist-strap) was provided to each subject to be worn during each exercise session of the 12-week intervention. The intervention was based on a previous study that demonstrated a compensatory response of roughly 1,000 kcal/day regardless of kcal expended per week (either 3,000 or 1,500 kcal) [101]. In the present investigation, subjects were instructed to exercise either 2- or 6-days per week (exercise group) or remain sedentary (control group). Subjects in the 2-day per week group were instructed to complete at least two exercise sessions per week (90 to 120 minutes per session), whereas the 6-day per week group was to complete at least six exercise sessions per week (40 to 60 minutes per session). Those in the exercise group were instructed to report back to the lab weekly to meet with the research staff where exercise sessions recorded on the Polar A-300 were downloaded using the PolarFlow™ software. During each download meeting session, research staff provided feedback to subjects on their amount of time and energy expended from each session's prior week. These meetings also allowed the research staff to evaluate the exercise sessions and track compliance with the intervention. Compliance was defined as completing at least 90% of the instructed exercise sessions per month. Subjects that did not complete at least 90% of expected exercise sessions per month were dropped from the study. The exercise session reports that were downloaded provided the amount of time the subject spent in each heart rate zone, which was used to calculate the energy expended during exercise (exercise energy expenditure, ExEE). The intensity was self-selected as long as subjects were in at least in HRR zone 1. Dietary habits were instructed not to be changed during the 12-week intervention.

3.2 Assessments

3.2.1 Physical Activity

At baseline, habitual, free-living physical activity was measured by an ActiGraph accelerometer (GT3X+ model; Pensacola, Florida) to ensure subjects were sedentary, i.e., not engaging in structured exercise, before baseline testing. Subjects wore the monitor at the waistline during all awake hours, apart from bathing and swimming. The monitor's data was recorded weekly to determine minutes of vigorous physical activity (VPA) with consecutive strings of zeros greater than 20 minutes or non-wear time, removed from recordings. Data of VPA was determined by using the Crouter et al. algorithm, and Freedson cut points. VPA was used to determine exercise behaviors instead of the more typical moderate to vigorous physical activity (MVPA), as non-exercise behaviors such as walking would be included in MVPA but not necessarily indicative of purposeful exercise. This was the case with many subjects who were part of a large University system and required to walk across a sprawling campus daily.

3.2.2 Rate of Energy Expenditure

The rate of energy expenditure at five different heart rate zones was calculated using a graded exercise treadmill test using the Trackmaster TMX428 Metabolic cart interface treadmill with integrated 12-lead ECG. Indirect calorimetry was used to analyze oxygen (O_2) consumption, and carbon dioxide (CO_2) expired. The initial start of the test included a five-minute warm-up walk at 0% grade and 3.0 mph. After completion, the treadmill grade was increased to 2.5% for three minutes and every three minutes after that until an approximate 10-beat peat per minute increase in heart rate was produced from the previous stage with speed unchanged at 3.0 mph. Subjects continued the test until a heart rate of 85% heart rate reserve (HRR) was achieved or if they could not continue. The rate of energy expenditure (kcal per minute) was determined by the Weir equation [102] for each heart rate zone. Precisely, the rate of energy expenditure (kcal

per minute) at different heart rate zones was calculated by regressing the average rate of energy expenditure during the last 30-seconds of each stage against the average heart rate from the last 30-seconds of the corresponding stage. Subjects completed the following test at baseline and at six-weeks to formulate a new regression equation and thus new values for the rate of energy expenditure for each stage to account for improvements in fitness when starting an exercise intervention. Using the average rate of energy expenditure at each heart rate zone and the time spent exercising in each zone (provided from Polar Heart Rate Monitor), the training-induced exercise energy expenditure (TrEE) of each session was calculated, which was used to determine total exercise energy expenditure (ExEE) and compensation index (CI).

3.2.3 Resting Energy Expenditure

REE was measured at baseline and post as this value was needed to calculate ExEE and alterations in metabolic activity. Indirect calorimetry (Quark RMR; Cosmed USA, Chicago, IL) with a ventilated canopy was used to measure REE. Participants were instructed to arrive fasted (~10-hr) and remain awake for the 45-minute test. REE was measured for 30-minutes after a 15-minute rest in the supine position. The additional 15-minutes were required to develop the steady-state, defined as <10% fluctuation in O_2 consumption and <5% fluctuation in the respiratory quotient (RQ), which is needed for a valid REE.O_2 consumed, and CO_2 produced determined 24-hour REE (kcal) using the Weir equation [102].

3.2.4 Body Composition

A GE Lunar iDXA machine measured body composition for each participant at baseline and post. The GE Lunar iDXA machine, performed using thick mode recommended by the software, provided a total body scan to obtain the absolute and relative measurements of total body and regional soft tissue masses such as fat mass (FM), fat-free mass (FFM), and mineral-free lean (MFL). iDXA scans were analyzed

using GE Lunar enCORE Software (13.60.033) with calibration performed before each session. From this assessment, FM and FFM measurements were obtained and used to calculate accumulated energy balance (AEB) since alterations in energy balance have been observed to correspond with changes in body composition [103].

3.2.5 Appetite-Regulating Hormones

The appetite-regulating hormone's concentrations were obtained by standard blood collection procedures at the outpatient wing of the University of Kentucky's CCTS hospital after a 10 to 14-hr overnight fast. Concentrations of ghrelin, leptin, GLP-1, and insulin were assessed before (fasting, minute 0) and after consumption of a standardized breakfast meal, that was 20% of the subjects' estimated energy needs. Selection of these specific hormones based on the most common hormones implicated in exercise-induced increases in appetite [13]. The estimated energy needs were found based on the subject's REE and the sedentary activity factor of 1.4. The standardized breakfast meal consisted of one Nutra-grain^{TM} bar and cornflakes with 2% milk (an unsweetened soymilk substitute was optional for lactose-intolerant participants). The completion of the meal consumption was instructed to be within 15 minutes; after consumption, the first blood draw initiation was initiated. The blood draws were completed in 15-minute increments 15, 30, 45, 60 for the first hour and 30-minute increments (90, 120, 150, 180) during the second hour. EDTA-coated and serum tubes were used to collect the blood samples. Serum insulin was measured with a chemiluminescent immunometric assay (Siemens), whereas ghrelin, leptin, and GLP-1 were measured using enzyme-linked immunosorbent assay (ELISA, Millipore, Phoenix Pharmaceuticals, Alpco).

3.2.6 Energy Compensation

To calculate compensation for energy expended during exercise, AEB was calculated from FM and FFM changes and converted to kcal equivalents. Gaining 1kg

FM and 1kg FFM reflected as 12,000 kcal and 1,780 kcal, respectively, whereas losing 1kg FM and 1kg FFM reflected as -9,417 kcal and -884 kcal, respectively [104, 105]. After calculating AEB, ExEE was calculated from training-induced energy expenditure (TrEE) with an addition of 15% excess post-exercise energy expenditure acquired after exercise sessions (TrEE * 0.15), and subtracting the basal energy expenditure (REE * 1.2) that would have occurred during the exercise session so not to include it twice [106]. The final equation to calculate ExEE is as follows: ExEE = (TrEE * 0.15) + (TrEE – training duration * (REE * 1.2)). CI was calculated to assess the percentage of ExEE compensated for. The total amount of kcal compensated was calculated first by adding AEB (a negative value if participants decreased body weight) to ExEE. In the following equation, (ExEE + AEB)/ExEE x 100%, the number of total kcal compensated was converted to form a percentage, referred to as percent kcal compensated, or CI. Thus, a positive CI depicts a negative energy balance less than ExEE (participants at least partially compensated for the energy they expended during exercise). A negative value indicates that energy balance is more negative than expected, or the participants lost more weight than energy expended. When CI equals zero, subjects lost the same weight as the energy they expended, i.e., they did not compensate.

3.3 Statistical Analysis

T-tests were performed to determine baseline group differences in sex, age, BMI, VPA, REE/kg FFM, RQ, VO_2 peak, and exercise training-induced variables (ExEE, AEB, and CI) at post-testing. The primary outcomes were CI, kcal compensated, percent body fat loss, and appetite-regulating hormone concentrations with interest in how these variables related to exercise dose defined as sessions per week, ExEE per week, time spent exercising per week, and exercise intensity (percent time spent exercising in HRR zones 3-5). Linear mixed-effects models were used to model the relationships between time point (12 weeks vs. baseline) and group over time (minutes 0 to 180) for the

concentrations of appetite-regulating hormones (leptin, ghrelin, GLP-1, and insulin). Post-prandial changes in appetite-regulating hormone concentrations were evaluated as changes in the area under the curve (delta-AUC), calculated by the trapezoidal rule. Over time group differences, between-group differences, and group-time interactions in primary outcomes were tested by repeated-measures two-way ANOVA, with sex and age included as covariates.

Additionally, ANCOVA analyses were performed for the delta-AUC of appetite-regulating hormones and body weight/FM; both bodyweight and FM were presented as percent change and raw values. Bivariate correlation analysis was used to calculate correlates of CI and percent body fat loss. Linear regression analyses were used to predict CI and percent body fat loss using leptin delta-AUC, ghrelin delta-AUC, exercise group (exercise frequency), time spent exercising per week, ExEE per week, and exercise intensity as independent variables. All analyses were performed in IBM SPSS Version 26 (IBM Corporation, Armonk, NY).

CHAPTER 4. Results

In Table 6, no differences in baseline characteristics (sex, age, BMI, VPA, REE/kg FFM, RQ, VO_2 peak) between groups. Exercise training-induced variables and differences in weekly ExEE, time spent exercising, and percent body fat loss are found in Table 7. All participants engaged in less than 90 minutes of VPA per week with an average of 47.73 ± 6.13 in the 6-day per week group and an average of 52.31 ± 4.62 in the 2-day per week group. As expected, the 6-day group expended more energy and exercised longer per week than the 2-day ($P \leq 0.05$). CI did not differ between groups ($P > 0.05$); as such, only the 6-day group lost FM, $P = 0.03$. The control group % body fat loss change was different from both exercise groups, $P < 0.05$. Results from the mixed-effects models indicated only ghrelin ($P = 0.03$) and leptin ($P < 0.01$) had significant group by time interactions, decreasing to a greater extent in 6d than 2d or control.

Changes over time and between groups for delta-AUC of the appetite-regulating hormones are presented in Table 8. Between-group changes for Leptin-delta-AUC in both the 6-day and 2-day groups were different from the control group. Changes over time (baseline to post) in leptin-delta-AUC were only different in the 6-day per week group ($P < 0.05$). No other hormones (delta-AUC) demonstrated significant changes over time or between groups.

Listed in Tables 9 and 10 are the results from the linear regression analyses predicting CI and percent body fat change. Leptin-delta-AUC was the only independent predictor of CI while controlling for percent body fat loss change and ExEE. Ghrelin-delta-AUC was the only independent predictor of percent body fat loss change when controlling for CI and ExEE.

Table 6. Baseline differences in demographics (sex, age, BMI) vigorous physical activity, and metabolic rates (REE/Kg FFM) of participants between groups (includes all randomized participants).

	6-day per week group N=19	2-day per week group N=20	Control N=14
Sex (% female)	68.40	85.00	78.80
Age (years)	29.32 ± 7.27	28.56 ± 5.85	26.00 ± 7.80
BMI[1]	29.00 ± 2.87	30.51 ± 3.47	29.36 ± 2.87
VPA[2]	9.08 ± 12.88	8.57 ± 17.45	12.91 ± 19.87
REE/Kg FFM[3]	31.52 ± 4.76	33.86 ± 4.75	33.37 ± 4.62
RQ[4]	0.93 ± 0.10	0.90 ± 0.09	0.92 ± 0.06
VO_2 Peak[5]	39.76 ± 4.56	38.45 ± 2.57	39.95 ± 4.84

Data as mean ± SD.

[1]BMI: Body Mass Index, kg/m^2.

[2]VPA: Minutes of VPA assessed objectively assessed via accelerometry using Freedson cut points.

[3]REE/Kg FFM: Resting energy expenditure per kg FFM, in kcal per 24-hr, assessed from indirect calorimetry. Calculated via the Weir equation from O_2 consumed and CO_2 produced.

[4]RQ: Respiratory quotient, CO_2 produced divided by O_2 consumed during resting energy expenditure test.

[5]VO_2 Peak: Estimated from submaximal exercise test, $mL \cdot kg^{-1} \cdot min^{-1}$.

Table 7. Resulting data from the exercise intervention between groups that exercised.

	6-day per week group N=15	*2-day per week group N=17*	*All participants N=32*
Exercise Time/week[1, *]	320.50 ± 20.40	188.80 ± 12.00	249.41 ± 16.85
% Time in Zone 3-5[2]	47.73 ± 6.13	52.31 ± 4.62	50.32 ± 3.69
% Time in Zone 1-2[3]	52.11 ± 5.68	47.69 ± 4.62	49.67 ± 3.69
ExEE/week[4, *]	2,753.50 ± 144.90	1,490.70 ± 122.10	2,041.68 ± 150.80
Kcal compensated/week[5]	1,309.86 ± 274.50	715.42 ± 268.60	961.39 ± 198.70
Total exercise time[6]	3,944.20 ± 242.80	2,265.40 ± 143.40	2,992.90 ± 202.20
Total ExEE[7]	33,091.00 ± 2,112.80	17,562.00 ± 1,547.70	24,291.00 ± 1,895.00
Total kcal compensated[8]	15,718.00 ± 3,294.1	8,585.00 ± 3,223.00	11,537.00 ± 2,384.20
AEB[9]	−16,789.00 ± 3,589.80	−8,977.30 ± 3,515.30	−12,363.00 ± 2,586.70
CI[10]	55.43 ± 10.16	49.31 ± 20.56	50.25 ± 12.27
Kg weight loss[11]	−1.04 ± 0.45^	−0.76 ± 0.60	−0.59 ± 0.38
% weight loss[12]	−1.48 ± 0.64^	−0.84 ± 0.66	−1.09 ± 0.45
Kg body fat loss[13, *]	−1.82 ± 0.39^	−0.64 ± 0.44	−0.58 ± 0.34
% Body fat loss[14, *]	−7.70 ± 2.04^*	−1.86 ± 1.27[#]	−4.43 ± 1.30
Delta REE/kg FFM[15]	1.06 ± 0.94	−1.45 ± 1.08	−0.38 ± 0.81

Table 7. (continued)

	6-day per week group N=15	*2-day per week group N=17*	*All participants N=32*
Delta RQ[16]	−0.11 ± 0.06	−0.09 ± 0.07	−0.09 ± 0.04

Data are mean ± SE, only individuals who completed intervention included.

*: Indicates significant differences between groups, P ≤ 0.05.

^: Indicates significant change over time (change different from zero), P ≤ 0.05.

*, #: Like symbols indicated significant differences between groups, P ≤ 0.05.

[1]Exercise time/week: Amount of time (min) spent exercising per week.

[2]% Time in zone 3-5: Percentage of time exercising spent in HR zones 3, 4, or 5 (70%–100% HRR).

[3]% Time in zone 1-2: Percentage of time exercising spent in HR zones 1 or 2 (50%–69% HRR).

[4]ExEE/week: Exercise energy expenditure (in kcal) per week.

[5]Kcal compensated/week: Energy (kcal) compensated for each week calculated by adding AEB + total ExEE together and dividing by 12.

[6]Total exercise time: Total amount of time spent exercising during the entire 12-wk intervention (in min).

[7]Total ExEE: Total exercise energy expenditure of the 12-wk intervention (in kcal).

[8]Total kcal compensated: Total amount of kcal compensated, calculated by adding AEB + total ExEE together.

[9]AEB: Accumulated energy balance, calculated from changes in bodily energy stores (changes in fat and lean mass) converted to kilocalorie equivalents.

[10]CI: Percentage of kcal compensated for, calculated as (ExEE + AEB) / ExEE.

[11]Kg weight loss: Kg of total body weight lost after the 12-wk intervention.

[12]% weight loss: Kg of weight loss divided by baseline body weight (in kg).

[13]Kg body fat loss: Kg of body fat lost after the 12-wk intervention.

[14]% body fat loss: Kg of body fat loss divided by baseline body fat (in kg).

[15]Delta REE/kg FFM: Changes in REE per kg of FFM from baseline to post (post value subtracted by baseline value).

[16]Delta RQ: Changes in respiratory quotient during rest from baseline to post (post value subtracted by baseline value).

Table 8. Comparing pre- and post-prandial differences between groups and over time of the changes in AUC for concentrations of Leptin, Acylated Ghrelin, GLP-1, and Insulin.

	6-day per week group N=12	*2-day per week group N=14*	*Control N=11*
Ghrelin ΔAUC	−5321.99 ± 4304.09	1778.38 ± 2114.07	−4028.67 ± 2440.11
Leptin ΔAUC	−998.57 ± 414.16 * #	−604.53 ± 617.98 ^	1118.31 ± 650.77 * ^
Insulin ΔAUC	−1090.49 ± 759.40	410.80 ± 625.16	315.39 ± 1184.69
GLP-1[1] ΔAUC	−27.10 ± 20.85	−19.12 ± 22.86	−25.90 ± 12.85

Data as mean ± SE.

*, ^: Like symbols indicated significant different between groups, $P \leq 0.05$.

#: Indicates significantly different from zero (change from baseline is significant), $P \leq 0.05$.

[1]GLP-1: Glucagon-Like Peptide 1

Table 9. Regression models predicting CI among exercise groups. The control group did not have a value for ExEE and thus did not have values for CI.

Effect	β	SE	P	Partial Correlation[1]
Full model of all predictors				
Intercept	47.87	27.85	0.10	
Leptin[2] ΔAUC	0.01	<0.01	<0.01	0.60 *
Exercise frequency[3]	23.98	23.01	0.17	0.31
Exercise time/week[4]	−0.13	0.11	0.24	−0.27
ExEE/week[5]	0.13	0.02	0.47	0.17
% Time in zones 3–5[6]	0.09	0.35	0.81	0.06
% body fat lost[7]	5.79	1.25	<0.01	0.73 *
Reduced model of significant predictors				
Intercept	86.42	7.05	<0.01	
Leptin[2] ΔAUC	0.01	<0.01	<0.01	0.64 *
% body fat lost[7]	4.28	0.88	<0.01	0.71 *

[1]Partial correlation also displayed.

*: Indicates significant correlation

[2]Leptin ΔAUC: Changes in area under the curve for changes in concentrations of leptin pre-meal (fasting) to 2-hrs post-prandial.

[3]Exercise frequency: Participants were randomly assigned to exercise 6-days per week or 2-days per week.

[4]Exercise time/week: Amount of time (min) spent exercising per week.

[5]ExEE/week: Exercise energy expenditure (in kcal) per week.

[6]% Time in Zone 3-5: Percentage of time exercising spent in HR zones 3, 4, or 5 (70%–100% HRR).

[7]% body fat loss: Kg of body fat loss divided by baseline body fat in kg.

Table 10. Regression models predicting percent body fat loss among exercise groups. The control group did not have values for many independent variables and predictors.

Effect	β	SE	P	Partial Correlation[1]
Full model of all predictors				
Intercept	5.62	4.78	0.26	
Leptin[2] ΔAUC	<0.01	<0.01	0.07	0.43
Ghrelin[3] ΔAUC	<0.01	<0.01	0.03	0.50 *
Exercise frequency[4]	0.23	4.00	0.95	0.01
Exercise time/week[5]	0.02	0.02	0.22	0.29
ExEE/week[6]	−0.01	0.03	0.05	−0.45 *
% Time in zones 3–5[7]	0.07	0.06	0.31	−0.25
Reduced model of significant predictors				
Intercept	5.80	3.19	0.08	
Ghrelin[3] ΔAUC	<0.01	<0.01	<0.03	0.44 *
ExEE/week[6]	−0.01	<0.01	0.01	−0.54 *

[1]Partial correlation also displayed.

*: Indicates significant correlation.

[2]Leptin ΔAUC: Changes in area under the curve for changes in concentrations of leptin pre-meal (fasting) to 2-hrs post-prandial.

[3]Ghrelin ΔAUC: Changes in area under the curve for changes in concentrations of leptin pre-meal (fasting) to 2-hrs post-prandial.

[4]Exercise frequency: Participants were randomly assigned to exercise 6-days per week or 2-days per week.

[5]Exercise time/week: Amount of time (min) spent exercising per week.

[6]ExEE/week: Exercise energy expenditure (in kcal) per week.

CHAPTER 5. Discussion

The present study evaluated aerobic exercise's effect at varying exercise frequencies on post-prandial hunger hormone responses after a 12-week exercise intervention. We evaluated the effect these hormonal changes have on the compensatory response to exercise and percent body fat loss change using a linear regression model to determine independent predictors of these hormonal changes. Determining these predictors can help reduce or slow the obesity epidemic by altering the way exercise intervention treatments are instituted. Recent research has indicated that exercise can alter appetite-regulating hormones; however, it is not known which variables predict these hormonal changes [2, 5, 8, 9]. Automatic compensatory responses to exercise can decrease the success of an exercise for weight loss intervention by resisting negative energy balance. These responses include decreases in resting and activity-induced energy expenditure [107, 108]. However, the primary compensatory response to an exercise-induced energy deficit is increased energy intake, controlled by the individual [1, 6, 19]. It is uncertain how appetite-regulating hormones affect energy compensation with exercise or other factors of the exercise program that influences these purported changes. From this evidence, we demonstrate the link between changes in appetite-regulating hormone concentrations, compensatory responses, and body fat change with exercise.

One of the hypotheses proposed in the present study was that increases in ghrelin concentrations and decreases of leptin, insulin, and GLP-1 concentrations in response to a meal would be greater when exercising 6-days per week than 2-days per week for 12 weeks did not hold. Only leptin was significantly different between groups, with the 6-day per week group decreasing to a greater extent than the 2-day per week group. This leptin change was most likely due to the 6-day per week group losing more body fat than the 2-day per week group. Many studies have demonstrated that leptin levels are

proportional to the degree of adiposity, with concentrations elevated among overweight and obese populations [8, 9]. However, since leptin is a satiety-inducing hormone, one may assume that greater increases in this hormone would reduce food consumption and improve the compensatory response to exercise. The present study demonstrated that greater leptin-delta AUC reductions predicted less energy compensation even when controlling for ExEE and body fat loss. Therefore, regardless of how much one exercises or how much fat one loses, the amount of leptin can predict the amount of kcal one compensates for in healthy and overweight to obese individuals. This may be due to exercise increasing leptin sensitivity, making it more effective as a satiety-inducing hormone.

The other hypothesis proposed in the present study that changes in appetite-regulating hormones after 12 weeks of exercise will predict body fat loss, with changes in ghrelin being negatively associated with body fat loss and leptin, GLP-1, and insulin being positively associated with body fat loss, only held with ghrelin. The present study observed changes in ghrelin-delta-AUC predicted percent body fat loss change even when controlling for CI and ExEE. Thus, greater increases in post-prandial ghrelin changes caused greater body fat loss, regardless of the length of exercise (ExEE) or the amount of kcal you compensate for (CI).

This study is not without limitations. The exercise sessions that participants performed were unsupervised. Therefore, it was possible that additional exercise not being recorded, or not strictly aerobic exercise, was undertaken; nevertheless, no evidence led to this suspicion. Sex differences were not observed in the study likely due to the greater sample number of females. Regarding female participants, another limitation was not assessing the stage of the menstrual cycle. The menstrual cycle stage has been indicated in recent literature to alter energy intake and energy expenditure; thus, affecting compensatory response calculations made for certain subjects [64].

CHAPTER 6. Conclusion

Several studies have demonstrated changes in appetite-regulating hormones after acute- and long-term or moderate and intense exercise. However, the amount of research on changes in the hormones and their influence on compensatory response to exercise is limited [10-17, 21, 25-28]. This can pose limitations to health care professionals when prescribing the most effective exercise regimen in promoting sufficient weight loss among overweight and obese individuals. Based on the present study, understanding the influence of the appetite-regulating hormones on compensatory responses to exercise is essential for a successful weight loss intervention.

From the results, leptin changes predict the amount of kcal one compensates for, regardless of the length of exercise or fat one loses. Being overweight and obese with a larger amount of FM than FFM diminishes the success of sufficient weight loss due to hormone imbalances that directly influence compensatory responses that can resist the maintenance of negative energy balance making weight loss a greater challenge [8, 9, 21]. These leptin reductions caused less energy compensation, whereas reductions of ghrelin caused greater body fat loss; thus, analyzing leptin and ghrelin concentrations may be beneficial for weight loss success paired with exercise. One would think that reductions in leptin would cause greater energy compensation; however, we observed that reductions in leptin’s concentration caused less energy compensation. This leptin observation can be described by decreased leptin resistance due to reduced leptin concentration; thus, increasing leptin's receptors' sensitivity. Several research investigations have proposed many mechanisms that explain this phenomenon of leptin resistance [109]. The common conclusion of the mechanism that plays a vital role in leptin resistance is alterations in cellular Ob-Rb receptor signaling [109]. Leptin resistance is analogous to insulin resistance, in which physiological feedback mechanisms limit Ob-Rb receptor signaling in obese states; thus, reducing the appetite-

regulating effects of leptin [109]. It is concluded that post-prandial changes in ghrelin and leptin are a crucial modulator in one’s success in an exercise for weight loss intervention, regardless of the length of exercises. Still, the physiological mechanisms that control compensatory responses are complex and could make it challenging to provide appropriate and effective treatment. The study's findings indicate the importance of the implications of these changes that can be a predictor for successful weight loss; however, future research is needed to evaluate the success of hormonal manipulation for sufficient weight loss among overweight and obese subjects.

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